

Fraud in Medical Research:

Emphasis on Statistical Aspects

Ted Colton, ScD

Professor & Chair Emeritus

**Department of Epidemiology &
Biostatistics**

A Continuum with Fuzzy Boundaries

Deliberate!

Fraud
Cheating
Misconduct

Questionable methods
Data torturing
Data dredging
Selective reporting
Selective non-reporting

Either

Ignorance, Naiveté
Carelessness, Sloppiness
Improper methods
Statistical 'fallacies'

Unintentional

Types of Fraud

- **Plagiarism** - not dealt with in this talk
- **Falsification** – data alteration
- **Fabrication** – made-up data

Motivation for Fraud

- Obtain a desired result, e.g. 'statistical significance'
- Monetary gain, enhancement of prestige
- Compensate for laziness, sloppiness in data collection
- Include subjects who would otherwise be excluded

Some Historical Instances of Fraud

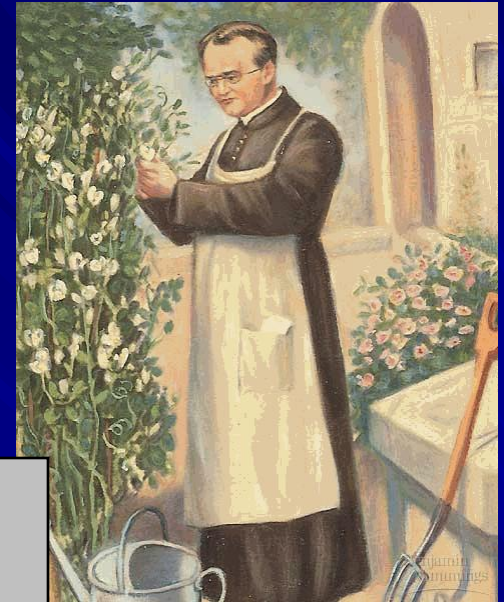
Gregor Mendel



Date: 1865

Place: Bohemia

Research: Genetics of garden peas



Sir Ronald Fisher

Sir Cyril Burt



Date: 1955-66

Place: Great Britain

Research: IQs of identical twins reared apart and reared together



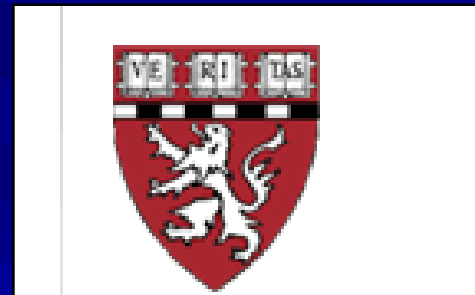
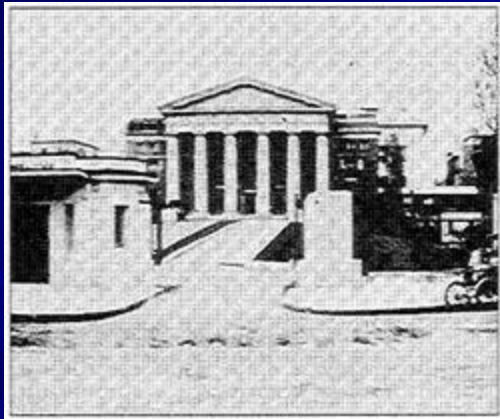
Leon Kamin

Dr. John Darsee

Date: 1981

Place: Harvard Medical School, Peter Bent Brigham Hospital

Research: Laboratory and animal studies of cardiovascular disease



Data Items in Clinical Trials Prone to Fraud

- Eligibility criteria
- Repeated measurements
- Adverse events
- Compliance
- Subject diaries

Questions for Consideration

1. How was fraud detected?
2. Why was fraud committed?
3. What have been the consequences of fraud?
4. Statistically, how do we handle data when some data are suspected or confirmed as fraudulent?
5. Can we use statistical methods to detect or confirm suspected instances of fraud?
6. What measures, if any, can we take to prevent future episodes of fraud?



Dr. Marc Strauss

Date: 1978

Place: Boston University Medical Center

Research: Multi-center clinical trials of cancer, ECOG

Dr. Roger Poisson

Date: 1992

Place: St. Luc's Hospital, Montreal

Research: Multi-center clinical trial of lumpectomy vs. radical mastectomy in treatment of breast cancer, NSABP



Chicago Tribune

Sunday, March 13, 1994

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Fraud in breast cancer study

★
By John Crewdson
TRIBUNE STAFF WRITER

PITTSBURGH—Federal investigators have documented more than a decade of fraud in some of the most important breast cancer research ever conducted, including a landmark 1985 study that established the relative safety of the operation known as lumpectomy and made it a common surgical procedure.

The organizers of the study privately assured investigators nearly two years ago that the fraud had not affected the "direction" of their

Doctor lied on data for decade

findings about lumpectomy, or any of the other major conclusions that since have been drawn from a complex of related breast cancer studies.

But Dr. Bernard Fisher, the Pittsburgh surgeon who heads the giant research consortium that changed the course of breast cancer treatment in this country, has yet to publish a promised reanalysis of

his data or to make any other public acknowledgment of the fraud.

Asked how soon, and in which journal, the reanalysis would be published, Fisher replied last week that "We don't know yet."

Responsibility for the fraud has been assumed by one of Fisher's principal collaborators, Dr. Roger Poisson, a professor of surgery at the University of Montreal. He

served for more than a decade as a major contributor to the U.S.-Canadian research group known as the National Surgical Adjuvant Breast and Bowel Project (NSABP).

Beginning in 1977, astonished investigators found, Poisson enrolled at least 100 of his cancer patients at the university's St. Luc Hospital in breast cancer studies conducted by Fisher even though they were ineligible on medical, technical or consensual grounds.

Poisson and his assistants then falsified or fabricated the medical

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Breast cancer data in doubt

Agency admits further review of flawed studies is needed

By John Crowdson
TRIBUNE STAFF WRITER

WASHINGTON—Less than a week after offering assurances that a Canadian researcher's falsification of data had not affected landmark breast cancer studies, the National Cancer Institute acknowledged Monday that it had no way of knowing whether those studies were influenced by the fraud.

It said that further review of the studies was required.

Monday's statement came after the NCI reacted to initial reports

of the fraud by hurriedly announcing that it had "reanalyzed all of the studies" that included data from the Montreal hospital where the fraud occurred and had confirmed "the original results and conclusions of the trials."

Those studies included key research that has since guided physicians and patients in their choice of breast cancer treatment. Officials emphasized that they have no reason to believe any of the studies is not valid.

But NCI officials now admit that they had not reanalyzed any of

the studies themselves, but had based their public comments on a summary of a partial reanalysis by the University of Pittsburgh, where the breast cancer study is headquartered.

"We have never reviewed all the primary data in these studies," said Dr. Michael A. Friedman, the NCI official in charge of the project.

"We reviewed the summary analysis that was provided to us." Since the NCI statement was issued, that document has been found to contain unexplained

omissions and what Friedman termed statistical "anomalies."

Paul van Nevel, an NCI spokesman, said Monday that last week's widely quoted statement was being rewritten. He said NCI officials had decided over the weekend to conduct their own analysis of raw data gleaned from thousands of breast cancer patients by the Pittsburgh group over nearly two decades.

The first study to be audited, Van Nevel said, probably would be Protocol B-06, the seminal 1985

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Breast cancer research project suspended

By John Crowdson
TRIBUNE STAFF WRITER

BETHESDA, Md.—The National Cancer Institute, struggling to cope with continuing fallout from revelations of fraud in breast cancer research, Tuesday suspended one of the nation's oldest and largest breast cancer research organizations from enrolling patients and ordered the replacement of the group's chairman and administrative staff.

Dr. Bernard Fisher, insisting that the results of his two decades of breast cancer research had not been compromised by the fraud, agreed to step down as chairman of the National Surgical Adjuvant Breast and Bowel Project. Fisher, 76, remains on the faculty of the University of Pittsburgh, where the project is headquartered.

The NCI, which said it also was taking steps to "correct deficiencies" in its own monitoring of such quasi-independent research consortiums, emphasized that thousands of patients enrolled in NSABP studies would continue to receive treatment and follow-up care.

The largest of the studies affected by the suspension is a controversial effort in which more than 10,000 healthy women at high risk for breast cancer are taking the anti-cancer drug tamoxifen in hopes it will reduce their susceptibility to the disease. Before his departure, Fisher had been pressing

to meet the study's targeted enrollment of 16,000.

The NCI, which provides the NSABP with \$8 million a year in federal funds, moved to restore public confidence in Fisher's landmark studies by auditing patient records in U.S. and Canadian medical centers, including a Montreal hospital where investigators uncovered what the NCI termed a "new irregularity."

According to an NCI statement, the NSABP's suspension, an action believed without precedent, was triggered by the organization's failure to conduct timely audits of the dozens of hospitals and medical centers where its patients are enrolled and treated and to report the results of those audits to NCI headquarters.

Investigators were said to have been astonished to discover just last week that NSABP officials had known since September of suspicious discrepancies in breast cancer data reported to NSABP by the St. Mary's Hospital Center in Montreal, but had said nothing to NCI even as the growing furor engulfed Fisher.

A St. Mary's official, reached by telephone Tuesday, confirmed that investigators from the NCI and the federal Office of Research Integrity, which polices science fraud, were installed in the hospital's board room, "looking at all the files of all patients who were part of the NSABP protocol."

Hours later, another Montreal hospital, Jewish General, said its NSABP patient records also were being reviewed by the cancer institute, but that it had been assured by a senior NCI official that it was "not suspected of wrongdoing."

The hospital noted in a statement that similar reviews already had been conducted at two U.S. institutions, Tulane and Louisiana State.

A Tulane spokeswoman told the Tribune that NCI auditors had completed their examination of records Monday and had promised an "expedited" report of their findings.

The Tribune reported two weeks ago that Dr. Roger Poisson, a surgeon at a third Montreal hospital, St. Luc, had falsified data on at least 100 patients enrolled in NSABP studies over more than a decade.

St. Luc and Jewish General, the teaching hospitals for the University of Montreal and McGill University, were the two largest contributors of patients to the 1985 NSABP study that established the safety and effectiveness of the surgical procedure known as lumpectomy.

While criticizing the NSABP for what it asserted was laxity in auditing patient records, the NCI also took partial responsibility, announcing that it had created a new branch to assess and monitor the compliance of groups like

the NSABP with federal research standards for quality assurance.

The NSABP will not be permitted to enroll new patients in any studies until the cancer institute completes what it described as "an intensive review" of the group's administrative procedures.

The quality assurance procedures of all other research groups are to be examined later, the NCI said.

The institute reiterated its belief that the falsifications presented "no cause for concern" about the current treatment of breast cancer, including the widely followed dictum that, for certain early cancers, the surgical procedure known as lumpectomy is as safe as the more disfiguring total mastectomy.

A reanalysis of some of Fisher's studies provided to NCI shows that their major conclusions are unchanged even after the tainted or questionable Canadian data is subtracted.

Statisticians estimated, however, that the "power" of the lumpectomy study had been reduced by the deductions to the point where it might no longer accurately predict the effect of a given treatment on one woman in every 15.

The reanalysis supplied by Pittsburgh is incomplete, and the NCI has asked a private Bethesda research firm to perform an independent reanalysis.

Nation

House panel told of flawed research

By Paul Recer
ASSOCIATED PRESS

Former head of cancer study testifies

WASHINGTON — At least 11 institutions falsified data, failed to enroll patients properly or misplaced key data in a national breast cancer research project, officials told Congress yesterday.

A reexamination of clinical trial records at 120 of the 500 institutions participating in the National Surgical Adjuvant Breast and Bowel Project have found what one official called "serious problems" at two sites in Pittsburgh, two in California, two in Montreal, two in New Orleans, one in Chicago and one in New York. The name of one institution was not disclosed.

Audit records of the other institutions are being examined, officials said.

One of the major studies by the project was to determine if breast-sparing therapy was successful in treating breast cancer. The

study concluded that lumpectomy, in which only the tumor is removed, followed by radiation is as good as mastectomy, in which the whole breast is removed, in saving the lives of breast cancer patients.

Though the original conclusion was based on studies including flawed data, the leader of the project has said that repeated analysis of the study, along with at least five other, unrelated studies, showed that lumpectomy is a successful therapy.

Testimony about the troubled, \$9 million research project was heard before a House subcommittee on oversight and investigations and included the first public testimony by Dr. Bernard Fisher, who until March directed the project. He took responsibility for what he called administrative errors.

Fisher was removed after it was dis-

closed that researchers at St. Luc Hospital and St. Mary's Hospital in Montreal had been falsifying data. Fisher had been in charge of the national cancer research effort headquartered at the University of Pittsburgh for 27 years.

The data falsification, which started in the 1980s at St. Luc, was known by project officials and by the National Cancer Institute for months before it became public.

Some of the problems have been known by auditors of the national research project for up to four years, yet Fisher and project officials have taken no action, said Rep. John Dingell, Democrat of Michigan, chairman of the House Energy and Commerce subcommittee.

"This matter is in part about failed responsibility," Dingell said. "It is in part

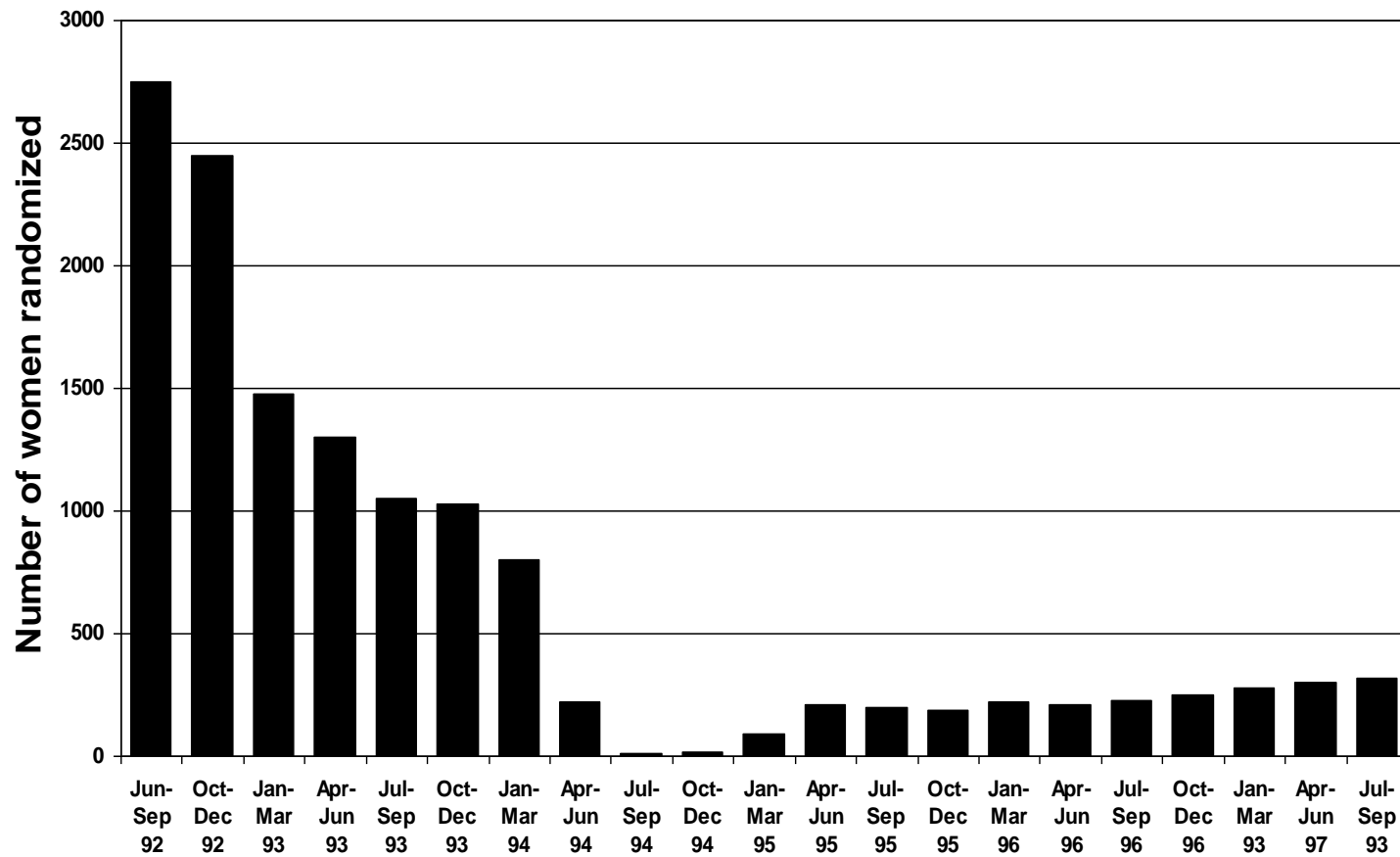
about failures of scientific integrity. But, above all, the question that should concern us most is the welfare of the thousands of women who at some considerable risk to themselves committed their lives and health to these studies."

At the Memorial Cancer Research Foundation in Los Angeles, investigators found inaccuracies in data starting in 1990. Though the problem was reported to leaders of the research project, no action was taken, Dingell said.

Asked to name a single incident in which he took action after an audit had found data problems at any institution, Fisher stammered into silence before replying, "My main issue would be to order my personnel to carry out their jobs."

"I take full responsibility for the administrative errors under my term," Fisher said. "But my main interest was to try to do the best science possible."

Breast Cancer Prevention Trial Accrual by Calendar Quarter





St. Mary's Hospital

Date: 1994

Place: St. Mary's Hospital, Montreal

Research:

Breast Cancer Prevention Trial, NSABP

NSABP[®]

*National Surgical Adjuvant
Breast and Bowel Project*

St. Mary's Incident – DSMB Recommendations

- A thorough audit of *all* BCPT subjects at St. Mary's.
- Include all St. Mary's subjects without irregularities in all analyses.
- Subjects with data falsification should continue on their assigned regimens unless there are safety issues.
- Conduct final analyses with *inclusion* and with *exclusion* of subjects with data falsification.
- Publication of trial findings should include full disclosure of instances of scientific misconduct.

Mr. Paul H. Kornak



Date: 2001

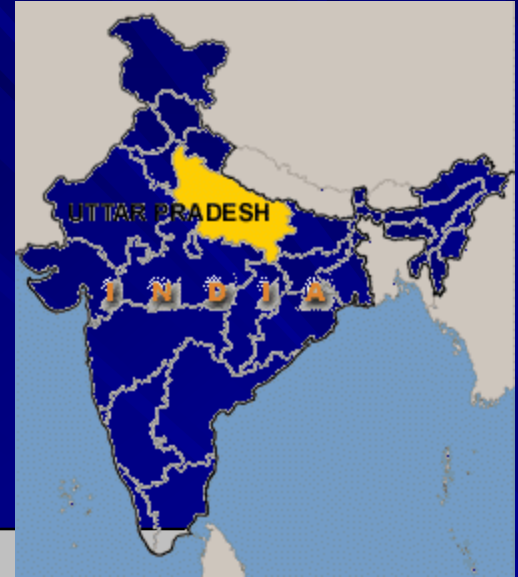
Place: Stratton VA Medical Center, Albany, NY

Research: The Iron (Fe) and Atherosclerosis Study (FeAST),
VA Cooperative Studies Program



UNITED STATES
DEPARTMENT OF VETERANS AFFAIRS

Dr. Ram Singh



Date: 1992

Place: Moradabad, Uttar Pradesh, northern India

Research: “Randomised controlled trial of cardioprotective diet in patients with recent acute myocardial infarction: results of one year follow up”, *BMJ*, 304:1015-19 (1992)



Dr. Stephen Evans

Conclusions

- Fraud in medical research has a long history and will undoubtedly continue into the future

Conclusions

- Fraud in medical research
 - Tarnishes the public image of medical research
 - Tarnishes the reputation of many innocent researchers and collaborators
 - Can impact negatively on other related ongoing research
 - Can virtually topple a large research organization

Conclusions

- Statistical methodology can aid in confirming fraud, but is insufficient as the sole detector of fraud.

Conclusions

- In multi-center clinical trials, the most common occurrences of fraud more likely produce 'noise' (bias towards the null) than invalid study findings.

Conclusions

- There is no proven intervention to prevent fraud, but education currently appears to hold promise to reduce its incidence and to moderate its consequences.

Take-home messages

- *Never* discard original research data.
- Missing data and outliers are very real phenomena in contemporary medical research.
- Have faith in the wondrously stochastic and random nature of real human data, features most difficult to capture with fraud.